Rising Sun Communications

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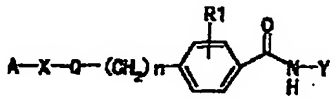
(unexamined)

CAUTION Post-Edited
Machine Translation

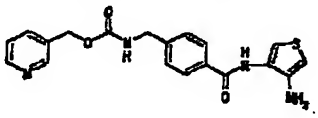
(54) Title of the invention
The benzamide derivative having histone deacetylase inhibition action.

(57) (Abstract) .
(Amended) .
(Method of Solution)
The benzamide derivative represented by following general formula (1) having histone deacetylase inhibition action.



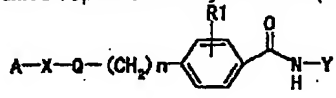
(1)

A concrete example of the compound comprises by formula showing bellow.



(effect)
The aforesaid benzamide derivative having histone deacetylase inhibition action is useful as therapy and/or improvement agent for disease involving proliferation of cell, effect potentiation drug of gene therapy or immunosuppressive drug. In particular effect is highly effective as antitumour agent in hematopoietic organ tumour, solid cancer.

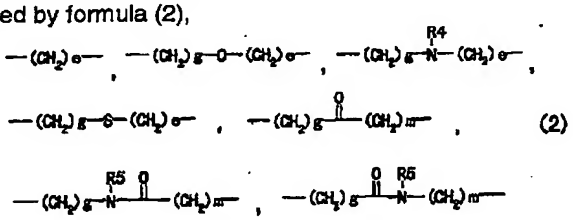
Patent Claims.
(Claim 1) .
A histone deacetylase inhibitor having as active ingredient, pharmacologically acceptable salt and benzamide derivative represented by formula (1),



(1)

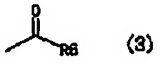
[In the formula, A denotes hydrogen atom, optionally substituted phenyl group or heterocycle. (containing as the substituent, 1-4 groups selected from the group comprising halogen atom, hydroxy group, amino group, nitro group, cyano group, alkyl group of carbon

number 1-4, alkoxy group of carbon number 1-4, amino alkyl group of carbon number 1-4, alkylamino group of carbon number 1-4, acyl group of carbon number 1-4, acylamino-group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4, perfluoro alkyloxy group of carbon number 1-4, carboxyl group, alkoxycarbonyl group of carbon number 1-4, phenyl group and heterocycle). X denotes direct bond or the structure represented by formula (2),



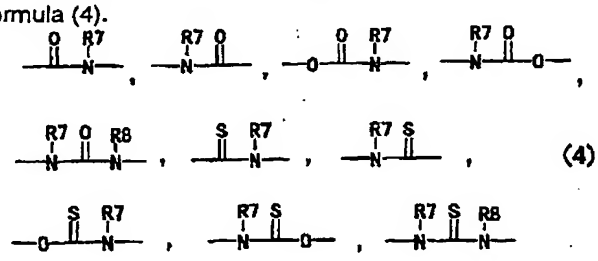
(2)

{In the formula, e, g and m respectively independently denote an integer of 0-4. R4 denotes hydrogen atom, optionally substituted 1-4C alkyl group or acyl group represented by formula (3),



(3)

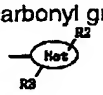
(wherein, R6 denotes optionally substituted 1-4C alkyl group, perfluoro alkyl group of carbon number 1-4, phenyl group or heterocycle). R5 denotes hydrogen atom or optionally substituted 1-4C alkyl group}. n denotes an integer of 0-4. Q denotes any of the structure represented by formula (4).



(4)

(In the formula, R7 and R8 respectively independently denotes hydrogen atom or optionally substituted 1-4C alkyl group), R1 denotes hydrogen atom, halogen atom, hydroxy group, amino group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, amino alkyl group of carbon number 1-4, alkylamino group of carbon number 1-4, acyl group of carbon number 1-4, acylimino-group of carbon number 1-4, alkylthio group of carbon

number 1-4, perfluoro alkyl group of carbon number 1-4, perfluoro alkyloxy group of carbon number 1-4, carboxyl group or alkoxycarbonyl group of carbon number 1-4. Y is formula (5).

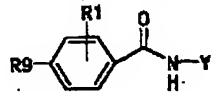


(5)

(In the formula, Het denotes heterocycle, R2 denotes hydrogen atom, halogen atom, hydroxy group, amino group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, amino alkyl group of carbon number 1-4, alkylamino group of carbon number 1-4, acyl group of carbon number 1-4, acylimino-group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4, perfluoro alkyloxy group of carbon number 1-4, carboxyl group or alkoxycarbonyl group of carbon number 1-4 and can be substituted at a possible position on heterocycle. R3 denotes hydroxy group or the amino group which is present adjacent to the location where benzamide bond connected to heterocycle].

(Claim 2)

A histone deacetylase inhibitor having as active ingredient benzamide derivative and pharmacologically acceptable salt in accordance with Claim 1 represented by formula (6).



(6)

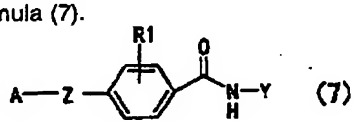
[In the formula, R9 denotes halogen atom, hydroxy group, amino group, hydroxyamino group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, amino alkyl group of carbon number 1-4, alkylamino group of carbon number 1-4, acyl group of carbon number 1-4, acylimino-group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4, perfluoro alkyloxy group of carbon number 1-4, carboxyl group or alkoxycarbonyl group of carbon number 1-4 and R1, Y have the same said meanings.]

(Claim 3)

A histone deacetylase inhibitor having as active ingredient benzamide derivative and pharmacologically acceptable salt in accordance with Claim 2, wherein Y is 4-aminothiophene-3-yl.

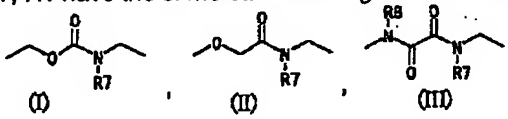
(Claim 4)

A histone deacetylase inhibitor having as active ingredient benzamide derivative and pharmacologically acceptable salt in accordance with Claim 1 comprising any of the structure represented by formula (7).



(7)

[In the formula, A, Y, R1 have the same said meanings. Z denotes formula (8).



(8)

(I) (II) (III)

(R7 and R8 has the same said meanings)]

(Claim 5)

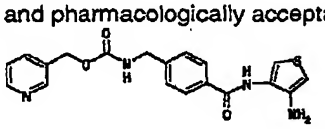
A histone deacetylase inhibitor having as active ingredient benzamide derivative and pharmacologically acceptable salt in accordance with Claim 4, wherein A is optionally substituted pyridyl group.

(Claim 6)

A histone deacetylase inhibitor having as active ingredient benzamide derivative and pharmacologically acceptable salt in accordance with Claim 5, wherein Y is 4-aminothiophene-3-yl.

(Claim 7)

A histone deacetylase inhibitor having as active ingredient benzamide derivative represented by formula (9) and pharmacologically acceptable salt.



(9)

(Claim 8)

A carcinostatic agent containing as effective ingredient at least one compound in accordance with any of Claims 1-7.

(Claim 9)
A drug which contains as effective ingredient at least one compound in accordance with any of Claims 1-7.

Detailed Description of the Invention
(0001)
(Technical Sphere of this Invention) .
This invention relates to a benzamide derivative having histone deacetylase inhibition action. More particularly this invention relates to the use as antitumour agent and other drugs on the basis of histone deacetylase inhibition action.

(0002)
(Technology of the Prior Art)
DNA forms complex with histone in nucleus of cell, and chromatin structures folded in high orders is formed, and it is held in an inert condition (Knezetic et al., Cell, 45: 95-104, 1986 and the like). When genetic transcription is performed in the nucleus, it is required that the structure thereof is derived into an unwound condition so that various transcription factors can be contacted with DNA (Felsenfeld et al., Cell, 86: 13-19, 1996). The relationship between acetylation of histone and activation of transcription has been reported in the past, but it has become clear that one of the actions causing changes in the structure leading to transcription activation is acetylation of histone (Hong et al., J. Biol. Chem., 268: 305-314, 1993 and the like). Moreover, histone acetylation enzyme (histone acetyl transferase) and histone deacetylase (histone deacetylase, HDA) are ones controlling acetylation thereof and importance thereof has recently been recognised (A. Csordas, Biochem. J., 265: 23, 1990 and the like). Sodium butyrate with which arrest of cell cycle and induction of differentiation had been confirmed for a long time is a representative HDA inhibitor (L.S. Cousens et al., J. Biol. Chem., 254: 1716, 1979 and the like), and the clinical use has also been attempted (Novogrodsky et al., Cancer, 51: 9-14, 1983 and Miller et al., Eur. J. Cancer Clin. Oncl II 23: 1283-1287, 1987). However, because the fundamental inhibiting activity is low and the in-vivo sustainability is also short, a high dosage is required to demonstrate an effect. Therefore an increase of sustainability has been attempted with a prodrug of butyric acid

(Zi-Xing et al. Cancer. Res., 54: 3494-3499, 1994 and Kasukabe et al., British J. Cancer, 75(6): 850-854, 1997 and the like). Moreover, a natural product, trichostatin A (TSA) has been found to derive an arrest in the cell cycle (Yoshida et al., Exp. Cell Res., 177: 122-131, 1988), proliferation stop, induction of differentiation (Yoshida et al., cancer Res., 47: 3688-3691, 1987), induction of cell morphology change and apotosis. As the mechanism thereof, TSA was confirmed to be a HDA inhibitor having high activity in vitro (Yoshida et al., J. Biol. Chem., 265: 17174, 1990). Moreover, the study of other HDA inhibitors has been continued, and an inhibitory action has been found with trapoxin(?) (Itazaki et al., J. Antibiot., 43(12): 1524-1534, 1990 and the like) and phenylbutyric acid (Carducci et al., Clin. Cancer Res., 2(2): 379, 1996 and the like). As those HDA inhibitors have cell cycle arrest and differentiation induction actions, application is anticipated primarily as a carcinostatic. Moreover, in addition, as far as HDA inhibitors are concerned, application is anticipated primarily as antitumour agent.

(0003)
In other words, as therapy / improvement drug of disease involving proliferation of cell, various applications such as for example therapy / improvement drug for autoimmune disease, dermatopathia, and infection (Darkin-Rattray et al., Proc. Natl. Acad. Sci. USA, 93: 13143-13147, 1996), moreover more efficient introduction of vector in gene therapy (Dion et al., Virology, 231: 201-209, 1997), expression facilitation of transgene (Chen et al., Proc. Natl. Acad. Sci. USA, 94: 5798-5803, 1997) have been tried. However, the inhibitors so far have not reached the level that are thoroughly satisfactory as a drug when stability, toxicity, drug kinetics or active strength are considered. So development of a drug which solves these problems is strongly desired.

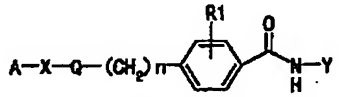
(0004)
Problems to be Overcome by this Invention.
The object of this invention is to put forward a compound useful as drug such as effect potentiation drug of gene therapy with improved problems of HDA inhibitor of prior art which is useful as therapy and/or improvement agent of disease involving proliferation of cell.

(0005)
Means to Overcome these Problems.

The these inventors carried out assiduous investigations to solve these problems, as a result confirmed that benzamide derivative had strong HDA inhibitory effect. This invention was completed on the basis of this discovery.

(0006)
In other words this invention comprises [1] a histone deacetylase inhibitor having as active ingredient, pharmacologically acceptable salt and benzamide derivative in accordance with Claim 1 represented by formula (1),

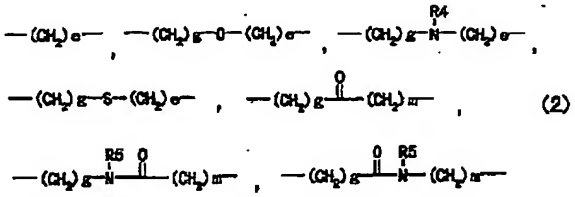
(0007)



(1)

[In the formula, A denotes hydrogen atom, optionally substituted phenyl group or heterocycle. (As the substituent, it contains 1-4 groups selected from the group comprising halogen atom, hydroxy group, amino group, nitro group, cyano group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, amino alkyl group of carbon number 1-4, alkylamino group of carbon number 1-4, acyl group of carbon number 1-4, acylamino-group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4, perfluoro alkyloxy group of carbon number 1-4, carboxyl group, alkoxycarbonyl group of carbon number 1-4, phenyl group and heterocycle) X denotes direct bond or the structure represented by formula (2),

(0008)



(2)

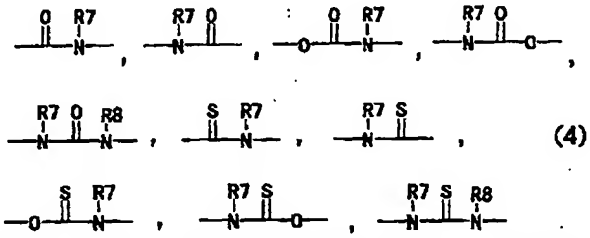
{In the formula, e, g and m respectively independently denote an integer of 0-4. R4 denotes hydrogen atom, optionally substituted 1-4C alkyl group or acyl group represented by formula (3),

(0009)


(3)

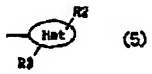
(wherein, R6 denotes optionally substituted 1-4C alkyl group, perfluoro alkyl group of carbon number 1-4, phenyl group or heterocycle) R5 denotes hydrogen atom or optionally substituted 1-4C alkyl group.} n denotes an integer of 0-4. Q denotes any of structure represented by formula (4).

(0010)


(4)

(In the formula, R7 and R8 respectively independently denotes hydrogen atom or optionally substituted 1-4C alkyl group), R1 denotes hydrogen atom, halogen atom, hydroxy group, amino group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, amino alkyl group of carbon number 1-4, alkylamino group of carbon number 1-4, acyl group of carbon number 1-4, acylimino-group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4, perfluoro alkyloxy group of carbon number 1-4, carboxyl group or alkoxycarbonyl group of carbon number 1-4. Y is formula (5).

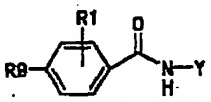
(0011)


(5)

(In the formula, Het denotes heterocycle, R2 denotes hydrogen atom, halogen atom, hydroxy group, amino group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, amino alkyl group of carbon number 1-4, alkylamino group of carbon number 1-4, acyl group of carbon number 1-4, acylimino-group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4, perfluoro alkyloxy group of carbon number 1-4, carboxyl group or alkoxycarbonyl group of carbon number 1-4 and can be substituted by a possible position on heterocycle. R3 denotes hydroxy group or the amino group which is present adjacent to the location where benzamide bond connected to heterocycle], moreover [2] a histone deacetylase inhibitor having as active

ingredient benzamide derivative in accordance with [1] and pharmacologically acceptable salt represented by the formula (6).

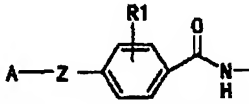
(0012)



(6)

[In the formula, R9 denotes halogen atom, hydroxy group, amino group, hydroxyamino group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, amino alkyl group of carbon number 1-4, alkylamino group of carbon number 1-4, acyl group of carbon number 1-4, acylimino-group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4, perfluoro alkyloxy group of carbon number 1-4, carboxyl group or alkoxycarbonyl group of carbon number 1-4 and R1, Y have the same said meanings]. moreover [3] a histone deacetylase inhibitor having as an active ingredient benzamide derivative and pharmacologically acceptable salt in accordance with [2] wherein Y comprises 4-aminothiophene-3-yl. Moreover [4] The histone deacetylase inhibitor having as active ingredient benzamide derivative and pharmacologically acceptable salt in accordance with [1] comprising any of the structure represented by formula (7).

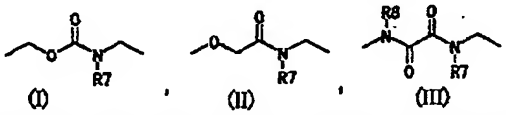
(0013)



(7)

[In the formula, A, Y, R1 have the same said meanings. Z denotes formula (8).

(0014)

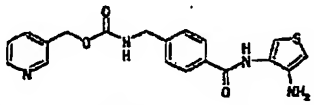


(8)

(R7 and R8 has the same said meanings)], moreover [5] a histone deacetylase inhibitor having as active ingredient benzamide derivative and pharmacologically acceptable salt in accordance with [4], wherein A is optionally substituted pyridyl group, moreover [6] a histone deacetylase inhibitor having as active ingredient benzamide derivative and pharmacologically acceptable salt in accordance with [5], wherein Y is 4-aminothiophene-3-

yl, moreover, [7] a histone deacetylase inhibitor having as active ingredient benzamide derivative represented by formula (9) and pharmacologically acceptable salt,

(0015)



(9)

moreover, [8] a carcinostatic agent which contains as effective ingredient at least one compound in accordance with any of [1]-[7], and moreover, [9] a drug which contains as effective ingredient at least one compound in accordance with any of [1]-[7].

(0016)
Conditions for carrying out this invention.
Hereinafter this invention is described in greater detail. As carbon number 1-4 stated in this invention, the carbon number per the unit substituent is denoted. In other words, in case of for example dialkyl substitution the carbon number 2-8 is denoted.

(0017)
As heterocycle in the compound represented by formula (1), a monocyclic heterocycle or a bicyclic fused heterocycle of 5 membered ring or 6 membered ring containing 1-4 nitrogen atoms or oxygen atoms or sulphur atoms, and as monocyclic heterocycle, for example pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, pyrrole, pyrazole, isooxazole, isothiazole, imidazole, oxazole, thiazole, piperidine, piperazine, pyrrolidine, quinacridine, tetrahydrofuran, morpholine, thiomorpholine and the like are nominated and as bicyclic condensed heterocycle, for example condensed pyridine ring such as quinoline, isoquinoline, naphthyridine, furopyridine, thienopyridine, pyrrolopyridine, oxazolo pyridine, imidazolo pyridine, thiazolopyridine and the like, benzofuran, benzo thiophene, benzimidazole and the like are nominated.

(0018)
As halogen atom, fluorine atom, chlorine atom, bromine atom, iodine atom are nominated.

(0019)

As alkyl group of carbon number 1-4, for example methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, t-butyl group are nominated.

(0020)
As alkoxy group of carbon number 1-4, for example methoxy group, ethoxy group, n-propoxy group, isopropoxy group, allyloxy group, n-butoxy group, Iso butoxy group, sec-butoxy group, t-butoxy group are nominated. As amino alkyl group of carbon number 1-4, for example aminomethyl group, 1-amino ethyl group, 2-aminopropyl group are nominated.

(0021)
As alkylamino group of carbon number 1-4, for example N-methylamino group, N,N-dimethylamino function, N,N-diethylamino group, N-methyl-N-ethylamino group, N,N-diisopropylamino group are nominated.

(0022)
As acyl group of carbon number 1-4, for example acetyl group, propanoyl group, butanoyl group are nominated.

(0023)
As acylimino-group of carbon number 1-4, for example acetylamino group, propanoyl amino group, butanoyl amino groups are nominated.

(0024)
As alkylthio group of carbon number 1-4, methylthio group, ethylthio group, propylthio group are nominated.

(0025)
As perfluoro alkyl group of carbon number 1-4, for example trifluoromethyl group, pentafluoro ethyl groups are nominated.

(0026)
As perfluoro alkyloxy group of carbon number 1-4, for example trifluoro methoxy group, pentafluoro ethoxy group are nominated.

(0027)
As alkoxycarbonyl group of carbon number 1-4, for example methoxycarbonyl group, ethoxycarbonyl group are nominated.

(0028)
As optionally substituted 1-4C alkyl group, for example methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, t-butyl group and one containing 1-4 groups selected from the group comprising halogen atom, hydroxy group, amino group, nitro group, cyano group, phenyl group, heterocycle as the substituent are nominated.

(0029)
As salt of the pharmacologically acceptable compound, salt of inorganic acid such as hydrochloric acid, hydrobromic acid, sulphuric acid, orthophosphoric acid used regularly in this sphere and salt of organic acid such as acetic acid, lactic acid, tartaric acid, malic acid, succinic acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluoroacetic acid, p-toluenesulphonic acid, methanesulphonic acid are nominated.

(0030)
The drug denotes therapy and/or improvement drug for such as dermatopathia, infection, allergic disease, autoimmune disease, vascular disease or gene therapy effect promoter in addition to carcinostatic. In the compound represented by formula (1), when asymmetric carbon is present, it can be present in a form of mixture of stereoisomerism form including different stereoisomerism form or the racemic form. In other words this invention includes various kinds of forms prescribed like these, but these can be used as the effective ingredient compound in the same way.

(0031)
Hereinafter typical compounds represented by formula (1) of this invention are exemplified in Table-1 (Table 1-Table 5). Moreover this invention is not restricted to these examples.

(0032)

(Table 1)

The representative compound (1) of general formula (7)

	A	Z 27=S 28=N	R1	Y		
				Het	R2	R3
1	pyridin-3-yl	I	-H	thiophen-3-yl	-H	$-NH_2$
2	pyridin-3-yl	I	-H	thiophen-3-yl	-H	-OH
3	pyridin-3-yl	I	-H	thiophen-3-yl	$-CH_3$	$-NH_2$
4	pyridin-3-yl	I	-H	thiophen-3-yl	$-CH_3$	-OH
5	pyridin-3-yl	I	-H	thiophen-3-yl	$-COCH_3$	$-NH_2$
6	pyridin-3-yl	I	-H	thiophen-3-yl	$-COCH_3$	-OH
7	pyridin-3-yl	I	-H	thiophen-3-yl	$-CF_3$	$-NH_2$
8	pyridin-3-yl	I	-H	thiophen-3-yl	$-CF_3$	-OH
9	pyridin-3-yl	I	-H	thiophen-3-yl	-Cl	$-NH_2$
10	pyridin-3-yl	I	-H	thiophen-3-yl	-Cl	-OH
11	pyridin-3-yl	I	-H	thiophen-3-yl	$-OCH_3$	$-NH_2$
12	pyridin-3-yl	I	-H	thiophen-3-yl	$-OCH_3$	-OH
13	pyridin-3-yl	I	-H	thiophen-3-yl	$-NHCH_3$	$-NH_2$
14	pyridin-3-yl	I	-H	thiophen-3-yl	$-NHCH_3$	-OH
15	pyridin-3-yl	I	-H	thiophen-3-yl	$-OCF_3$	$-NH_2$
16	pyridin-3-yl	I	-H	thiophen-3-yl	$-OCF_3$	-OH
17	pyridin-3-yl	I	-H	thiophen-3-yl	$-COOCH_3$	$-NH_2$
18	pyridin-3-yl	I	-H	thiophen-3-yl	$-COOCH_3$	-OH
19	pyridin-3-yl	II	-H	thiophen-3-yl	-H	$-NH_2$
20	pyridin-3-yl	II	-H	thiophen-3-yl	-H	-OH

(0033)

(Table 2)

The representative compound (2) of general formula (7)

	A	Z RY=H RB=H	R1	Y		
				Het	R2	R3
E1	pyridin-3-yl	II	-H	thiophen-3-yl	$-CH_3$	$-NH_2$
22	pyridin-3-yl	II	-H	thiophen-3-yl	$-CH_3$	-OH
23	pyridin-3-yl	II	-H	thiophen-3-yl	$-COCH_3$	$-NH_2$
24	pyridin-3-yl	II	-H	thiophen-3-yl	$-COCH_3$	-OH
25	pyridin-3-yl	II	-H	thiophen-3-yl	$-CF_3$	$-NH_2$
26	pyridin-3-yl	II	-H	thiophen-3-yl	$-CF_3$	-OH
27	pyridin-3-yl	II	-H	thiophen-3-yl	-Cl	$-NH_2$
28	pyridin-3-yl	II	-H	thiophen-3-yl	-Cl	-OH
29	pyridin-3-yl	II	-H	thiophen-3-yl	$-OCH_3$	$-NH_2$
30	pyridin-3-yl	II	-H	thiophen-3-yl	$-OCH_3$	-OH
31	pyridin-3-yl	II	-H	thiophen-3-yl	$-NHCH_3$	$-NH_2$
32	pyridin-3-yl	II	-H	thiophen-3-yl	$-NHCH_3$	-OH
33	pyridin-3-yl	II	-H	thiophen-3-yl	$-OCF_3$	$-NH_2$
34	pyridin-3-yl	II	-H	thiophen-3-yl	$-OCF_3$	-OH
35	pyridin-3-yl	II	-H	thiophen-3-yl	$-COOCH_3$	$-NH_2$
36	pyridin-3-yl	II	-H	thiophen-3-yl	$-COOCH_3$	-OH
37	pyridin-3-yl	III	-H	thiophen-3-yl	-H	$-NH_2$
38	pyridin-3-yl	III	-H	thiophen-3-yl	-H	-OH
39	pyridin-3-yl	III	-H	thiophen-3-yl	$-CH_3$	$-NH_2$
40	pyridin-3-yl	III	-H	thiophen-3-yl	$-CH_3$	-OH

(0034)

(Table 3)

The representative compound (3) of general formula (7)

	A	Z R7=H R8=H	R1	Y		
				Het	R2	R3
40	pyridin-3-yl	III	-H	thiophen-3-yl	$-CH_3$	-OH
41	pyridin-3-yl	III	-H	thiophen-3-yl	$-COCH_3$	$-NH_2$
42	pyridin-3-yl	III	-H	thiophen-3-yl	$-COCH_3$	-OH
43	pyridin-3-yl	III	-H	thiophen-3-yl	$-CF_3$	$-NH_2$
44	pyridin-3-yl	III	-H	thiophen-3-yl	$-CF_3$	-OH
45	pyridin-3-yl	III	-H	thiophen-3-yl	-Cl	$-NH_2$
46	pyridin-3-yl	III	-H	thiophen-3-yl	-Cl	-OH
47	pyridin-3-yl	III	-H	thiophen-3-yl	$-OCH_3$	$-NH_2$
48	pyridin-3-yl	III	-H	thiophen-3-yl	$-OCH_3$	-OH
49	pyridin-3-yl	III	-H	thiophen-3-yl	$-NHCH_3$	$-NH_2$
50	pyridin-3-yl	III	-H	thiophen-3-yl	$-NHCH_3$	-OH
51	pyridin-3-yl	III	-H	thiophen-3-yl	$-OCF_3$	$-NH_2$
52	pyridin-3-yl	III	-H	thiophen-3-yl	$-OCF_3$	-OH
53	pyridin-3-yl	III	-H	thiophen-3-yl	$-COOCH_3$	$-NH_2$
54	pyridin-3-yl	III	-H	thiophen-3-yl	$-COOCH_3$	-OH
55	pyridin-3-yl	I	-H	thiophen-2-yl	-H	$-NH_2$
56	pyridin-3-yl	II	-H	thiophen-2-yl	-H	$-NH_2$
57	pyridin-3-yl	III	-H	thiophen-2-yl	-H	$-NH_2$
58	pyridin-3-yl	I	-H	pyridin-2-yl	-H	$-NH_2$
59	pyridin-3-yl	I	-H	pyridin-2-yl	-H	$-NH_2$
60	pyridin-3-yl	I	-H	pyridin-2-yl	-H	$-NH_2$

(0035)

(Table 4) The representative compound (4) of general formula (7)

	A	Z X7=N L8=N	R1	Y		
				Het	R2	R3
61	pyridin-3-yl	1	-H	pyridin-3-yl	-H	-NH2
62	pyridin-3-yl	1	-H	pyridin-3-yl	-H	-NH2
63	pyridin-3-yl	1	-H	pyridin-3-yl	-H	-NH2
64	pyridin-3-yl	1	-H	pyridin-4-yl	-H	-NH2
65	pyridin-3-yl	1	-H	pyridin-4-yl	-H	-NH2
66	pyridin-3-yl	1	-H	pyridin-4-yl	-H	-NH2
67	pyridin-3-yl	1	-H	pirazin-2-yl	-H	-NH2
68	pyridin-3-yl	1	-H	pyrimidin-4-yl	-H	-NH2
69	pyridin-3-yl	1	-H	pyridazin-3-yl	-H	-NH2
70	pyridin-3-yl	1	-H	N-methyl-pyrrol-3-yl	-H	-NH2
71	pyridin-3-yl	1	-H	pyrrol-2-yl	-H	-NH2
72	pyridin-3-yl	1	-H	thiazol-2-yl	-H	-NH2
73	pyridin-3-yl	1	-H	piperidin-3-yl	-H	-NH2
74	pyridin-3-yl	1	-H	quinolin-5-yl	-H	-NH2
75	pyridin-3-yl	1	-H	isoquinolin-8-yl	-H	-NH2
76	pyridin-3-yl	1	-H	benzofuran-4-yl	-H	-NH2
77	pyridin-3-yl	1	-H	indol-4-yl	-H	-NH2
78	pyridin-3-yl	1	-H	benzothiophen-4-yl	-H	-NH2
79	pyridin-3-yl	1	-H	benzimidazol-4-yl	-H	-NH2
80	pyridin-3-yl	1	-H	thiophen-3-yl	-H	-NH2

(0036)

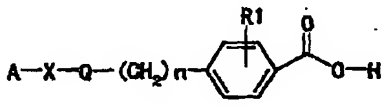
(Table 5)

The representative compound (5) of general formula (7)

	A	Z X7=N X8=N	R1	Y		
				Het	R2	R3
81	pyridin-4-yl	II	-H	thiophen-3-yl	-H	-NH2
82	pyrazin-2-yl	III	-H	thiophen-3-yl	-H	-NH2
83	pyrimidin-4-yl	I	-H	thiophen-3-yl	-H	-NH2
84	pyridazin-3-yl	II	-H	thiophen-3-yl	-H	-NH2
85	N-methyl-pyrrol-3-yl	III	-H	thiophen-3-yl	-H	-NH2
86	pyrrol-2-yl	I	-H	thiophen-3-yl	-H	-NH2
87	thiazol-2-yl	II	-H	thiophen-3-yl	-H	-NH2
88	piperidin-3-yl	III	-H	thiophen-3-yl	-H	-NH2
89	quinolin-5-yl	I	-H	thiophen-3-yl	-H	-NH2
90	isoquinolin-6-yl	II	-H	thiophen-3-yl	-H	-NH2
91	benzofuran-4-yl	III	-H	thiophen-3-yl	-H	-NH2
92	indol-4-yl	I	-H	thiophen-3-yl	-H	-NH2
93	benzothiophen-4-yl	II	-H	thiophen-3-yl	-H	-NH2
94	benzimidazol-4-yl	III	-H	thiophen-3-yl	-H	-NH2
95	pyridin-3-yl	I	-CH3	thiophen-3-yl	-H	-NH2
96	pyridin-3-yl	II	-Cl	thiophen-3-yl	-H	-NH2
97	pyridin-3-yl	III	-OCH3	thiophen-3-yl	-H	-NH2
98	pyridin-3-yl	I	-COCH3	thiophen-3-yl	-H	-NH2
99	pyridin-3-yl	II	-COOCH3	thiophen-3-yl	-H	-NH2
100	pyridin-3-yl	III	-NHCOCH3	thiophen-3-yl	-H	-NH2

The compound of this invention can be produced by process such as for example following. The compound of this invention can be obtained by subjecting the compound represented by formula (10)

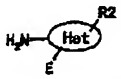
(0037)



(10)

[In the formula, A, Q, X, R1 and n have the same said meanings] and the compound represented by formula (11)

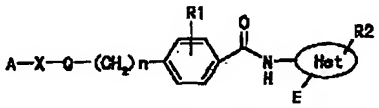
(0038)



(11)

[In the formula, R2 and Het have the same said meanings. E denotes amino group protected with protecting group used in ordinary peptide forming reaction such as t-butoxycarbonyl group or functional group which can be readily converted into amino group such as nitro group or azido group, or hydroxy group protected with protecting group used in ordinary peptide forming reaction such as benzyl group, and is bonded to location adjacent to amino group] to condensation reaction, eliminating protecting group or converting into amino group of thereby obtained compound represented by formula (12)

(0039)



(12)

(In the formula, A, Q, X, R1, R2, E, Het and n have the same said meanings).

(0040)

As for the compound represented by formula (10) and the compound represented by formula (11), a commercial product or already known compound can be used. Moreover, in the case of novel compound, it can be produced by application of synthesis method of well known compound. Condensation reaction of formula (10) and formula (11) can be put into effect by amide bond forming reaction in ordinary peptide, for example process of active ester or mixed acid anhydride or acid chloride. For example, it can be carried out by condensing carboxylic acid component and phenols such as 2,4,5-trichlorophenol, pentachlorophenol, 4-nitrophenol and the like or N-hydroxy compound such as N-hydroxysuccinimide, N-hydroxybenzotriazole and the like in the presence of dicyclohexylcarbodiimide, thereby converting into active ester, and thereafter condensing with amine component.

(0041)

Moreover, it can be carried out by reacting carboxylic acid component with oxalyl chloride, thionyl chloride, phosphorus oxychlorides and the like, thereby converting into acid chloride, and thereafter condensing with amine component. Moreover, it can be carried out by reacting carboxylic acid component with chlorocarbonic acid isobutyl or methanesulphonyl chloride and the like, thereby converting into acid anhydride, and thereafter condensing with amine component.

(0042)
Furthermore, aforesaid condensation reaction can be carried out by using peptide condensation reagent alone such as dicyclohexylcarbodiimide, N,N-carbonyldiimidazole, diphenyl phosphoric acid azide, diethyl phosphoric acid cyanide, 2-chloro-1,3-dimethyl imidazoloninum chloride and the like.

(0043)
The reaction is carried out at -20 to +50 degrees usually for 30 minutes to 48 hours. As the solvent used, for example, alcohols such as methanol, ethanol and the like or a mixture thereof are nominated in addition to aromatic hydrocarbon species such as benzene, toluene and the like, ethers such as tetrahydrofuran, dioxane, diethyl ether and the like, halogenated hydrocarbons such as methylene chloride, chloroform and the like, N,N-dimethylformamide. In accordance with requirements organic base for example triethylamine or pyridine is added and is reacted.

(0044)
Benzamide derivative having histone deacetylase inhibition action of this invention is useful as therapy and/or improvement agent of disease involving proliferation of cell, effect potentiation drug of gene therapy or immunosuppressive drug.

(0045)
Wherein, as a disease to be involved with proliferation of cell, malignant tumour, autoimmune disease, dermatopathia, infection, vascular disease, an allergic disease, gastrointestinal tract injury, hormonal disease, diabetes mellitus are nominated.

(0046)

As malignant tumour, in addition to hematopoietic organ tumours such as acute leukaemia, chronic leukaemia, malignancy lymphoma, multiple myeloma, macroglobulinemia, solid tumours such as colon cancer, brain tumour, head cervix cancer, breast cancer, lung cancer, cancer of the esophagus, gastric cancer, hepatoma, gallbladder cancer, bile duct cancer, pancreatic carcinoma, insula pancreatica cell cancer, kidney cell cancer, adrenal cortex cancer, tumour of the urinary bladder, prostatic cancer, testis tumour, ovary cancer, uterine cancer, carcinoma villosum, cancer of the thyroid, bad carcinoid tumour, skin cancer, malignant melanoma, osteosarcoma, soft tissue sarcoma, neuroblastoma, Wilms tumour and retinoblastoma are nominated.

(0047)
As autoimmune disease, rheumatism, nephritis, diabetes mellitus, systemic lupus erythematosus, human autoimmune lymphocytotic lymphadenopathy, immunoblastic lymphadenopathy, Crohn's disease and ulcerative colitis are nominated.

(0048)
As dermatopathia, psoriasis, acne, eczema, atopic dermatitis, parasitic dermatosis, alopecia, pyogenic dermatosis and skin sclerosis are nominated.

(0049)
As infection, diseases caused by infection of such as by various bacteria, viruses or parasites are denoted.

(0050)
As vascular disease, arteriosclerosis or restenosis therapeutic drug is nominated.

(0051)
As effect potentiation of gene therapy, more efficient introduction of gene vector, expression facilitation of transgene are nominated. Moreover subject disease of this invention is not necessarily restricted to these.

(0052)
The effective ingredient compounds of this invention are useful as drug, and these are used in a form of general medical formulation. Formulation is prepared using diluent of for

example filler, expander, binding agent, moisturizing agent, disintegrating agent, surface active agent, lubricant or excipient which are usually used. As this drug formulation, various forms can be selected corresponding to the therapy object and as representative thereof, tablet, pill, powder, liquid medicine, suspending agent, emulsion, granule, capsule agent, injection (liquid medicine, suspending agent) and suppository and the like are nominated.

(0053)
When it is formed into a tablet, various ones which is known well in the prior art as a carrier in this sphere, can be widely used. As example thereof, for example excipient such as lactose, dextrose, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, and the like, binding agent such as water, ethanol, propyl alcohol, single syrup, dextrose liquid, starch liquid, gelatine solution, carboxymethyl cellulose, shellac, methyl cellulose, polyvinylpyrrolidone and the like, disintegrating agent such as dried starch, sodium alginate, agar powder, carmellose calcium, starch, lactose, disintegration depressant such as refined sugar, cacao butter, hydrogenation oil, absorption promoter such as quaternary ammonium salt group, sodium lauryl sulphate and the like, moisturising agent such as glycerine, starch and the like, adsorbent such as starch, lactose, kaolin, bentonite, colloidal silicic acid, lubricant such as talc, stearate, polyethyleneglycol and the like can be used. Furthermore, as for a tablet, it can be made into coated tablet of ordinary agent in accordance with requirements, for example sugar coated tablet, gelatine encapsulation tablet, enteric-coated encapsulation tablet, film coating tablet or bilayer tablet, multilayer tablet.

(0054)
When it is formed into pill, ones well known in prior art in this sphere as a carrier, can be widely used. As example thereof, for example excipients such as crystalline cellulose, lactose, starch, hardening vegetable oil, kaolin, talc and the like, binding agent such as powdered gum Arabic, tragacanth powder, gelatine and the like, disintegrating agent such as carmellose calcium, agar and the like are nominated.

(0055)
Capsule agent is prepared by mixing the effective ingredient compound with above-mentioned various carriers according to conventional method, and packing into hard gelatine capsule, soft capsule and the like.

(0056)
When it is prepared as injection, it is preferred that liquid medicine, emulsion and suspending agent are sterilised and are isotonic with blood, and when it is formed into these, ones conventionally used in prior art in this sphere as diluent, for example water, ethanol, macrogol, propylene glycol, ethoxylation isostearyl alcohol, polyoxyisosteary alcohol, polyoxyethylene sorbitan fatty acid ester species can be used. In this case, sodium chloride, dextrose or glycerine of necessary quantity may be contained in drug formulation to prepare an isotonic solution, and moreover ordinary solubiliser, buffer agent, analgesic and the like may be added.

(0057)
When it is formed into suppository, ones well known in prior art as a carrier can be widely used. As example thereof, for example semi-synthetic glyceride, cacao butter, esters of higher alcohol, higher alcohol, polyethyleneglycol and the like are nominated.

(0058)
Furthermore colorant, preservative, flavour, flavour agent, sweetener and other drug can be contained in the drug formulation in accordance with requirements.

(0059)
The quantity of the effective ingredient compound which should be contained in these drug formulations of this invention is not restricted in particular and suitably selected from a wide range, but it is usually about 1-70 wt.% and preferably made into about 5-50 wt.% in the formulation composition.

(0060)
As for the administration method of these drug formulation of this invention, there are no restrictions in particular and it is administered by the methods that suits various formulation, age of patient, sex, degree of disease and other conditions. For example, in the cases of tablet, pill, liquid medicine, suspending agent, emulsion, granule and capsule agent, it is orally-administered, and in the case of injection, it is administered intravenously by itself or by being mixed with ordinary fluid replacement such as glucose, amino acid, and furthermore it is administered intramuscularly, subcutaneously or intraperitoneously by itself in accordance with requirements. In the case of suppository, it is administered in rectum.

(0061)
Dosage of these drug formulation of this invention is suitably selected by application, age of patient, sex, degree of disease and other conditions, but it is usually made into about around 0.0001-100 mg as the quantity of the effective ingredient compound per day per 1 kg weight. Moreover, it is desirable that the effective ingredient compound is contained by about 0.001-1,000 mg range in the formulation of administration unit form.

(0062)
The compound and salts thereof represented by formula (1) of this invention do not demonstrate toxicity in dosage that demonstrates pharmacological effect.

(0063)
(Example)
Below this invention is described in greater detail with Example, but this invention is not restricted to these.

Example 1.
Synthesis of N-(4-aminothiophene-3-yl)-4-methoxy benzamide
(1-1) 2,5-dibromo-3,4-dinitrothiophen 3.0 g (9 mmol) were added to concentrated hydrochoric acid 60 ml, and tin 6.5 g (54 mmol) were added. After generation of hydrogen stopped, it was left to stand overnight at room temperature. The precipitated solid was separated by filtration, and the filtrate was concentrated to about 20 ml. It was cooled with ice, and the precipitated crystals were recovered by filtration, and obtained crystals were washed with ether, and 3,4-diamino thiophene tin chloride dihydrochloride 0.39 g (10 %) was obtained.
1H NMR (270 MHz, DMSO-d6) delta ppm: 5.9 (br. s)

(1-2) 3,4-diamino thiophene tin chloride dihydrochloride 0.39 g (0.87 mmol) and p-anisoyl chloride 74 mg (0.43 mmol) were suspended in chloroform, and triethylamine 1 ml was added under ice-cooling. It was returned to room temperature, and it was left to stand overnight. This was introduced into 0.3 N hydrochloric acid and was extracted with CHCl3. Aqueous layer was neutralised with NaOH, and the crystals were recovered by filtration. The crystals were dissolved in CHCl3/MeOH and dried with MgSO4. Thereafter it was

filtered, and concentrated, and the target N-(4-aminothiophene-3-yl)-4-methoxy benzamide 40 mg (19 %) was obtained as crystals.
M.p. 126 deg C (dec.)
1H NMR (270 MHz, DMSO-d6) delta ppm: 4.9 (2H, br.s), 6.13 (1H, d, J = 3.7 Hz), 7.05 (2H, d, J = 8.8 Hz), 7.46 (1H, t, J = 3.7 Hz), 7.93 (2H, d, J = 8 Hz), 9.53 (1H, s).

(0064)
Example 2.
Synthesis of 4-amino-N-(4-aminothiophene-3-yl) benzamide
(2-1) 3,4-diamino thiophene tin chloride, dihydrochloride 2.33 g (7 mmol) and p-nitrobenzoyl chloride 648 mg (3.5 mmol) were suspended in chloroform, and triethylamine 5 ml were added under ice-cooling. It was returned to room temperature, and it was left to stand overnight. This was introduced into dilute sulphuric acid and was extracted with CHCl3. Aqueous layer was neutralised with NaOH, and the crystals were recovered by filtration. The crystals were dissolved in CHCl3/MeOH and were refined with short column, and the target N-(4-aminothiophene-3-yl)-4-nitrobenzamide 40 mg (5 %) was obtained as crystals.
1H NMR (270 MHz, DMSO-d6) delta ppm: 4.9 (2H, br.s), 6.15 (1H, d, J = 3.7 Hz), 7.54 (1H, d, J = 3.7 Hz), 8.15 (2H, d, J = 8 Hz), 8.37 (2H, d, J = 8 Hz), 9.97 (1H, s)

(2-2) N-(4-aminothiophene-3-yl)-4-nitrobenzamide 0.186 g (0.71 mmol) was suspended in methanol 1 ml and concentrated hydrochoric acid 1 ml, and stannous chloride 402 mg (2.1 mmol) was added and it was stirred at room temperature, thereafter left to stand overnight. Ice was added, and it was neutralised with 3N NaOH and was extracted with CHCl3. Organic layer and the solid were refined with silica gel column, and the target 4-amino-N-(4-aminothiophene-3-yl) benzamide 35 mg (21 %) was obtained as crystals.
M.p. 130 deg C (dec.)
1H NMR (270 MHz, DMSO-d6) delta ppm: 4.8 (2H, br.s), 5.7 (2H, br.s), 6.11 (1H, d, J = 3.7 Hz), 6.59 (2H, d, J = 8 Hz), 7.41 (1H, d, J = 3.7 Hz), 7.68 (2H, d, J = 8 Hz), 9.2 (1H, s)
IR(KBr)cm-1; 3387, 1603, 1506, 1405, 1286, 1185, 845, 772.

(0065)
Example 3.
Synthesis of N-(4-aminothiophene-3-yl)-4-hydroxyamino benzamide

N-(4-aminothiophene-3-yl)-4-nitrobenzamide 0.04 g (0.152 mmol) was dissolved in methanol 5 ml, and it was hydrogenated with Pd/C. Catalyst was separated by filtration, and the liquid was concentrated, and the crystals were obtained. These were washed with chloroform, and next dried, and the target N-(4-aminothiophene-3-yl)-4-hydroxyamino benzamide of 20 mg (53 %) was obtained.
M.p. 150 deg C (dec.)
1H NMR (270 MHz, DMSO-d6) delta ppm: 4.85 (2H, br.s), 6.11 (1H, d, J = 3.7 Hz), 6.87 (2H, d, J = 8 Hz), 7.44 (1H, d, J = 3.7 Hz), 7.80 (2H, d, J = 8 Hz), 8.57 (1H, s), 8.78 (1H, s), 9.4 (1H, s)
IR(KBr)cm-1; 3281, 1605, 1507, 1286, 1182, 847, 767.

(0066)
Example 4.
Synthesis of N-(3-aminopyridine-2-yl)-4-amino benzamide
(4-1) 4-nitrobenzoyl chloride 1.86 g were added to dioxane solution of 2-amino-3-nitropyridine 1.33 g, and it was heated under reflux.
Thereafter, dioxane was elliminated by distillation, and precipitated crystals were recrystallised with ethyl acetate/methanol, and N-(3-nitro-2-pyridyl-4-nitrobenzamide 1.74 g was obtained (60 %).
M.p. 215-216 deg C
1H NMR (270 MHz, DMSO-d6) delta ppm: 7.58 (1H, dd, J = 5,8 Hz), 8.23 (2H, d, J = 9 Hz), 8.38 (2H, d, J = 9 Hz), 8.48 (1H, dd, J = 1.5, 8 Hz), 8.79 (1H, dd, J = 1.5, 5 Hz)

(4-2) N-(3-nitropyridine-2-yl)-4-nitrobenzamide 1.0 g was suspended in a mixed solvent of DMF 4 ml and methanol 12 ml, and 10 % palladium carbon was hydrogenated as catalyst. Catalyst was separated by filtration, and the solvent was concentrated, and it was crystallised with methanol, and N-(3-aminopyridine-2-yl)-4-amino benzamide 0.69 g (76 %) was obtained.
M.p. 162-163 degC
1H NMR (270 MHz, DMSO-d6) delta ppm: 4.92 (2H, br.s), 5.75 (2H, s), 6.58 (2H, d, J = 9 Hz), 7.04 (1H, dd, J = 5,8 Hz), 7.17 (1H, d, J = 6.6 Hz), 7.73 (1H, d, J = 5 Hz), 7.77 (2H, d, J = 9 Hz), 9.96 (1H, s).

(0067)

Example 5.

Synthesis of N-(4-aminothiophene-3-yl)-4-{N-(pyridine-3-yl-methoxycarbonyl) aminomethyl} benzamide

4-{N-(pyridine-3-yl-methoxycarbonyl) aminomethyl} benzoic acid 208 mg was suspended in methylene chloride 6.2 ml, and oxalyl chloride 0.32 ml was added under ice-cooling. It was stirred at room temperature for 30 minutes, and thereafter dried to a solid under reduced pressure. The obtained 4-{N-(pyridine-3-yl-methoxycarbonyl) aminomethyl} benzoyl chloride was condensed in the same way as in Example 2, and N-(4-aminothiophene-3-yl)-4-{N-(pyridine-3-yl-methoxycarbonyl) aminomethyl} benzamide 55 mg (20 %) was obtained.

Mp. 170-174 deg C.

1H NMR (270 MHz, DMSO-d6) delta ppm: 4.33 (2H, d, J = 5.9 Hz), 4.91 (2H, br.s), 5.15 (2H, s), 6.18 (1H, d, J = 3.7), 7.44 (2H, d, J = 8.1), 7.55 (1H, d, J = 2.7), 7.83 (1H, d, J = 8.1) 7.94 (2H, d, J = 8.1), 8.01 (1H, m), 8.58 (1H, d, J = 3.7), 8.64 (1H, s), 9.67 (1H, s).

IR(KBr)cm-1: 3222, 3029, 1713, 1651, 1555, 1481, 1419, 1266, 1129, 1024, 982, 856, 793, 708.

(0068)

Example 6.

Synthesis of N-(4-aminothiophene-3-yl)-4-{N-(2-nitrobenzene sulphonyl) amino} benzamide

It was reacted in the same way as in Example 5 using 4-{N-(2-nitrobenzene sulphonyl) amino} benzoic acid, and N-(4-aminothiophene-3-yl)-4-{N-(2-nitrobenzene sulphonyl) amino} benzamide was obtained.

1H NMR (270 MHz, DMSO-d6) delta ppm: 6.10 (1H, d), 7.22 (2H, d, J = 8 Hz), 7.45 (1H, d), 7.8-7.9 (4H, m), 8.0-8.1 (2H, m), 9.54 (1H, s)

IR(KBr)cm-1: 3100, 1609, 1541, 1507, 1347, 1164, 853, 778.

(0069)

Pharmacological test example 1 (histone deacetylase inhibition action).

(1) Preparation of [3H] acetyl histone

K 562 cells (10 power 8 cells) were labelled with [3H] n-sodium butyrate, and histone was extracted according to process of Yoshida (J. Biol. Chem., 265, 17174, 1990).

(2) Partial purification of histone deacetylase

Nucleus collected from K 562 cell (2.5 x 10 power 8) was extracted according to process of Yoshida et al. (J. Biol. Chem., 265: 17174, 1990), and partial purification of histone deacetylase was carried out from the extract thereof using MonoQ HR5/5 (Pharmacia company) with a concentration gradient of NaCl of 0-1 M.

(3) Measurement of histone deacetylase inhibition activity
It was reacted for 10 minutes at 37 degrees in 50 µl Buffer A [composition: 5 mM potassium phosphate (pH 7.5), 5 % glycerol, 13 mM EDTA] containing 100 µg/ml [3H] acetyl histone prepared in (1) and histone deacetylase fraction 2 µl prepared in (2). The reaction was stopped by addition of 2.5 N hydrochloric acid, and thereafter 550 µl ethyl acetate was added, vortex and centrifugation were carried out, and 400 µl ethyl acetate layer was collected in scintillation vial, 2 ml scintillator was added and radioactivity of [3H] acetic acid which was freed by reaction was measured. Measurement of histone deacetylase inhibition activity was determined by sultably diluting the test compound with buffer A after dissolution with DMSO, and adding to the reaction system, and the concentration of drug induced 50 % enzyme inhibition (IC50: µM) was determined. Below experimental results are shown in Table-2 (Table 6).

(0070)
(Table 6)
Table-2: Histone deacetylase inhibition activity

	Activity value (IC50: µM)
Compound of Example 1	12
Compound of Example 2	17
Compound of Example 3	9
Compound of Example 4	86
Compound of Example 5	4
Compound of Example 6	8
Sodium butyrate	190

(0071)
Advantages Afforded by this Invention.

Benzamide derivative having histone deacetylase inhibition action of this invention is useful as therapy and/or improvement agent of disease involving proliferation of cell, effect potentiation drug of gene therapy or immunosuppressive drug. It is highly effective as carcinostatic in particular and is effective for hematopoietic organ tumour and solid cancer.

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